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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/734,613	12/13/2000	Marianne Bruggemann	37945-0009	3627

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	18

DATE MAILED: 07/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/734,613	BRUGGEMANN, MARIANNE	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 16-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 16-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *17* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 4/28/03 has been entered. Claims 14-15 and 30-34 have been canceled. Claims 1-13 and 16-29 are currently under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Priority

The previous office action indicated that the applicant has not filed a certified copy of the GB 9823930.4 application as required by 35 U.S.C. 119(b). The applicant has not responded to this issue, or provided a copy of the priority document. Priority to the GB 9823930.4 application cannot be perfected in the absence of the certified copy of the priority document. In the absence of a certified copy of the priority document, the effective filing date of the instant application is November 3, 1999.

Claim Rejections - 35 USC § 103

The rejection of claims 1-13 and 16-29 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,162,963 (12/19/00), filed on 6/5/95, and hereafter referred to as Kucherlapati et al., in view of Mendez et al. (1997) Nat. Genet., Vol. 15, 146-156 and Popov et al. (1996) Gene, Vo. 177, 195-201 is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that the in order to make a prima facie case of obviousness the office must provide specific evidence that the reference(s) teach each element of the claimed invention and that there exists suggestion/motivation to combine the references, citing *In re Vaeck, I re Dow Chemical Co.*, and *W.L. Gore v. Garlock, Inc.* The applicant also states that the evidentiary support must be based on the contents of the prior art and not rest on conclusory statements or subjective beliefs, citing *In re Lee*. In response, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Further, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of

the cited references must be viewed in light of these factors. Finally, please note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988). The previous office action provided a detailed description of where the claim limitations are taught or suggested by the combination of Kucherlapati et al., Mendez et al., and Popov et al. and provided specific motivation derived from the express teachings of Kucherlapati et al. and Popov et al. for combining the teaching of the prior art to arrive at applicant's claimed invention, see paper no. 15, pages 4-6.

Specifically, the applicant argues that Kucherlapati does not provide an enabling disclosure for making transgenic mice that have polynucleotides encoding human lambda light chains. The applicant argues that Kucherlapati's statement that transgenic mice can be made with human lambda light chains only represents an invitation to try to make these mice and that "obvious to try" is not an appropriate standard for the basis of an obviousness rejection. The applicant further argues that Mendez et al. also does not teach transgenic mice with human lambda light chains and that while Popov does teach the human Ig lambda YAC, Popov does not provide a concrete example of a transgenic mouse that comprises human Ig lambda chains.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Furthermore, the test for

combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). In the instant rejection, the office is aware that none of Kucherlapati, Mendez, and Popov individually teach all the elements of the invention as claimed. Therefore, these references have been cited in a 103 rejection. The previous office action cited Kucherlapati et al. for teaching methods of making transgenic mice which comprise various germline segments of the human Ig loci in order to produce mice capable of reproducing the normal human antibody repertoire in response to antigen (Kucherlapati, columns 3-4). In particular, Kucherlapati teaches that transgenic mice can be produced from murine embryonic stem cells modified to include YACs using spheroplast fusion techniques (Kucherlapati et al., columns 13-16). Specifically, Kucherlapati teaches that a number of different transgenic mice can be produced using their methods including mice which have one or both of the murine endogenous light chain and/or heavy chain loci inactivated by homologous recombination, and which further contain human immunoglobulin heavy chain and/or human light chain genes (Kucherlapati et al., columns 11-12). Kucherlapati et al. further teaches that the human light chain genes can be either human kappa light chain genes or human lambda light chain genes or both kappa and lambda light chain genes (Kucherlapati et al., column 11, lines 30-36). Kucherlapati et al. further teaches various human heavy chain and light chain YACs useful for

making transgenic mice (Kucherlapati, columns 29-33). Finally, Kucherlapati et al. provides particular motivation for making a mouse with disrupted expression of both endogenous Ig heavy and light chain genes, and which comprises human heavy chain, kappa light chain, and lambda light chain loci by teaching that such a mouse, ".. would allow for the production of purely human antibody molecules without the production of host of host/ human chimeric antibodies" (Kucherlapati et l., column 11, lines 30-36). Therefore, while not specifically exemplifying the production of a human lambda light chain transgenic mouse, Kucherlapati et al. provides substantial teachings as to how to make human immunoglobulin light chain transgenic mice using YACs and clearly suggests making a human lambda light chain transgenic mouse. Mendez et al. was cited to supplement Kucherlapati et al. by teaching transgenic mice which have disrupted endogenous Ig heavy chain and light chain loci, and which further have incorporated YACs comprising contiguous germline segments of the human Ig heavy chain and kappa light chain loci (Mendez et al., pages 146 and 154-155). In particular, Mendez et al. teaches that in mice with one allele of the smaller Ig YACs, an equal distribution of human kappa and murine lambda light chain gene expression was observed (Mendez et al., page 153, column 1). Mendez et al. also teaches that human antibody diversity and repertoire in the xenomice strains recapitulates that seen in humans (Mendez et al., pages 153-154). It was further noted that the human Ig heavy chain YAC utilized by Mendez includes Cμ, Cδ, and Cγ genes (Mendez et al., page 148). Mendez et al. was not cited to teach the incorporation of human lambda light chains genes, but rather to supplement the teachings of Kucherlapati regarding the production of transgenic mice which have disrupted

endogenous Ig heavy chain and light chain loci, and which further have incorporated YACs comprising contiguous germline segments of the human Ig heavy chain and kappa light chain loci. Popov et al. was cited to supplement Kucherlapati et al. by teaching the construction of a 420 kb YAC which contains 380 kb of the unrearranged germline human Ig lambda light chain locus (Popov et al., page 195). The YAC described by Popov is the exact YAC used by applicants. Popov et al. further provides motivation for using the YAC to produce transgenic mice useful for structure-function studies of the human Ig lambda locus (Popov et al., page 200, column 2). Popov et al. therefore supplies the essential teachings of the human lambda YAC that are missing from Kucherlapati and Mendez. Kucherlapati et al. and Mendez provide all the necessary disclosure for making transgenic mice using YACs and both Kucherlapati et al. and Popov et al. suggest making a human lambda light chain transgenic mouse. Thus, based on the motivation provided by Kucherlapati to make transgenic mice comprising germline segments of the human Ig lambda light chain loci, and the motivation provided by Popov et al. to use a 420 kb YAC comprising 380 kb of the human lambda light chain loci to make transgenic mice, it would have been *prima facie* obvious to the skilled artisan to use the 420 kb YAC described by Popov in the methods of making transgenic mice taught by Kucherlapati et al.. Further, based on the successful use of the methods taught by Kucherlapati to produce human Ig transgenic mice as taught by Mendez et al., the skilled artisan would have had a reasonable expectation of success in using the YAC taught by Popov et al. to introduce human lambda light chain genes into the germline of a mouse. As noted above, obviousness does not require absolute predictability of success; for

obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

The applicant further argues that an obviousness rejection can be overcome by a showing that (i) there are elements not taught by the references, (ii) there is a teaching away or no reasonable expectation of success, or (iii) the applicants have demonstrated unexpected results, citing *U.S. v. Adams Gillette Co.* v *S.C. Johnson & Son, Inc.*, and *Bausch & Lomb, Inc. v. Barnes-Hind Hydrocurve*. Applicant's arguments regarding the specific teachings of the references have been addressed in the preceding paragraph. Applicant's remaining arguments rest on applicant's assertion that none of the cited references provide a reasonable expectation that the lambda translocus would be able to compete equally with the endogenous mouse kappa locus and that the high level of expression of the human lambda genes in the transgenic mice represents unexpected results over the prior art. In response, it is noted that only claims 4 and 27 place any limitation on the expression of expression of the human lambda light chains in relation to kappa light chains. Claims 1-3, 5-13, and 16-26 do not recite a limitation concerning the comparative expression of lambda chains versus kappa chains. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, please note that claim 27, which recites a transgenic mouse carrying human lambda light chain genes in which expression of the human lambda locus is equal to or greater than that of a kappa locus, is broad and reads on a transgenic mouse wherein the endogenous kappa light chain is disrupted such that the expression

of human lambda light chain would necessarily be greater than that of a kappa locus. Further, regarding applicant's allegation of "unexpected results", the MPEP states that the arguments of counsel cannot take the place of evidence in the record . *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results. MPEP 716.01(c). Therefore, applicant's arguments regarding "unexpected results" are not compelling in the absence of evidence in the form of a declaration or affidavit.

However, it has been noted that Popov et al. in fact teaches the exact human lambda light chain YAC used by the applicant's in their working examples. Kucherlapati et al. in view of Mendez and Popov provides sufficient motivation and expectation of success in making a transgenic mouse using the same 380 kb YAC used by applicants. Any expression properties of this 380 kb YAC are inherent to the structure of the YAC. Further, it is noted that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. *In re Skoner*, et al. 186 USPQ 80 (CCPA). Finally, in regards to Mendez et al., Mendez has been cited for teaching that xenomouse I, which contains a small human light chain YAC, exhibits an equal distribution of kappa and lambda light chains. The YAC used in xenomouse I was close in size to the 380kb YAC of Popov et al. The applicant argues that Mendez et al. teaches away from a human pattern of light chain expression by teaching that xenomouse II shows mouse-like regulation of light chain utilization, citing Mendez at page 148, column 2. However, Mendez et al. on page 148, column 2, makes no statement regarding light chain utilization. Further, the YAC

used in xenomouse II is substantially larger than that taught by Popov, >800 kb versus 380 kb. Therefore, the argument that Mendez teaches away from the instant invention does not appear to be supported by the actual teachings of Mendez et al.

Thus, for reasons of record as discussed in detail above, the rejection of claims 1-13 and 16-29 under 35 U.S.C. 103 stands.

Claim Rejections - 35 USC § 112

The rejection of claims 4, 7-11, and 27-29 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to claims 4, 7, and 27.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER